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Attorney's Docket No. 9448-50

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Leonard
Serial No.: 10/041,916
Filed: January 8, 2002

Confirmation No.: 4094
Group Art Unit: 1616
Examiner: Badio, B.

For: SYNTHESIS OF A MIXTURE OF SULFATE ESTROGENS USING A SULFURTRIOXIDE COMPLEX

Date: November 3, 2004

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' REPLY BRIEF PURSUANT TO 37 C.F.R. §41.41

Sir:

This Reply Brief is filed to respond to the issues raised by the "Response to Argument" portion of the Examiner's Answer mailed September 3, 2004. Appellants submit that, for at least the reasons discussed in Appellants' Appeal Brief mailed May 21, 2004, and Appellants' clarifications provided below, the pending claims are not obvious in view of the cited references. Appellants incorporate each of the arguments and positions in the Appeal Brief in the present Reply Brief as if set forth fully herein. In the interests of brevity, these arguments and positions will not be reproduced below.

1. Claim Recitations in Claims Do Distinguish Over Cited References

Appellants agree with the Examiner's assessment that Simoons et al. (U.S. Pat. No. 4,154,820) and Raijmakers et al. (U.S. Pat. No. 5,998,639) do not teach the claimed process steps of reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts. Appellants also note that Claim 1 includes the recitations "adding a stabilizing amount of tris(hydroxymethyl)aminomethane and (c) recovering the stable composition comprising the mixture of sulfated estrogens and tris(hydroxymethyl)aminomethane." These recitations are also not taught or suggested by Simoons et al. or Raijmakers et al. Appellants further note that Claim 15 includes the recitations of reacting sulfur trioxide-trimethylamine with the mixture of alkali metal salts of estrogens in an apolar, aprotic solvent to provide a mixture of sulfated alkali metal salts of estrogens; (c) adding a stabilizing amount of

tris(hydroxymethyl)aminomethane; and (d) recovering the stable composition comprising the mixture of sulfated estrogens and tris(hydroxymethyl)aminomethane" which is not taught or suggested by Simoons et al. or Raijmakers et al. The Examiner notes that Raveendranath et al. (U.S. Pat. No. 5,288,717) proposes "a process for the production of the alkali metal 8,9-dehydroestone sulfate esters and their stabilized compositions." *See,* Raveendranath et al. at col. 1, lines 43-46. However, the Examiner apparently fails to recognize that Raveendranath et al. specifically states that the "process of this invention differs from methods generally involved in the sulfation of steroids which are carried out by treatment of the steroid with amine-sulfurtrioxide complexes followed by treatment with a cation exchange resin mediated by strong alkaline bases, preferably in hydroxylic solvents. **Those reported methods for sulfation of steroids proved ineffective** in the sulfation of 8,9-dehydroestrone." Appellants note that the bases used in Raijmakers et al. are stronger bases than those used in the present application. Appellants note that they utilize tris(hydroxymethyl)aminomethane which has a pKa of approximately 8.1 while pyridine, which is used in Raijmakers et al. is 5.2. Accordingly, Appellants submit that Raveendranath et al. teaches away from Raijmakers et al. as one of skill in the art would not use a stronger base after being informed that such a base previously proved ineffective.

2. Mischaracterization of Shah et al. (U.S. Pat. No. 6,525,039)

Appellants note that Shah et al. (U.S. Pat. No. 6,525,039) includes as one of the named inventor, one of the named inventors of Raveendranath et al. Yet, Shah et al. merely proposes the formation of various compounds of pharmaceutically acceptable salts of single estrogen sulfate esters or alkali metal salts of **a single estrogen sulfate ester**. *See*, Shah et al. at col. 1, lines 65-66. The formation of the sulfated estrogen ester sodium salt proposed by Shah et al. involves the simultaneous reaction of an estrogen with sodium hydride, a triethylamine-sulfurtrioxide complex, and a sodium hydroxide solution to **one** particular alkali metal salt of an estrogen sulfate ester. *See,* Shah et al. at Scheme 1 and Example 1. Shah does not teach or suggest the reaction of a **mixture** of alkali metal salts of estrogens with a sulfur trioxide complex. In fact, despite having the technology and expertise of Raveendranath et al. and the knowledge contained in Bender et al. (U.S. Pat. No.

5,998,638) (in which Shah was also an inventor), which does not even propose the sulfation of an alkali metal salt of estrogen, and the previous cited references, the named inventors of Shah et al. focused on a **single estrogen sulfate ester**. These inventors, those of skill in the art, never contemplated a process for producing a mixture of sulfated estrogens wherein the process involves reacting a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens. Accordingly, Appellants submit that there is no motivation in the prior art to combine the teachings of these references and render the claims of the present application obvious.

Conclusion

In summary, Appellants respectfully submit that, with respect to Claims 1-19, a prima facie case of obviousness under 35 U.S.C. § 103 has not been established. Accordingly, Appellants respectfully request that the present rejections be reversed.

If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact Applicants' attorney at the address or telephone number given herein.

The Examiner is authorized to charge Deposit Account No. 50-0220 for any additional fee which may be required.

Respectfully submitted,

Jarett K. Abramson
Registration No. 47,376

CERTIFICATE OF EXPRESS MAIL

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I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Katie A. Chung